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EXAMINER	
UNDERDAHL, THANE E	

ART UNIT	PAPER NUMBER
1651	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/560,317	LEENDERS ET AL.	
	Examiner	Art Unit	
	THANE UNDERDAHL	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 October 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10, 12-13* is/are pending in the application.

4a) Of the above claim(s) *8 and 9* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7, 10, 12-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

This Office Action is in response to the Applicant's reply received 10/13/09. Claims 1-10 and 12-13 are pending. Claims 8 and 9 are withdrawn. Claim 11 is cancelled. No claims have been amended. Claims 12 and 13 are new. Claims 1-7 and 10-13 are considered in this Office Action.

Objection to References Filed Without IDS

The Applicant's response includes three Non-patent Literature references without an IDS. This is not in compliance with 37 CFR 1.98. Specifically 37 CFR 1.98 (a)(1) requires the following: (1) a list of all patents, publications, applications, or other information submitted for consideration by the Office; (2) U.S. patents and U.S. patent application publications listed in a section separately from citations of other documents; (3) the application number of the application in which the information disclosure statement is being submitted on each page of the list; (4) a column that provides a blank space next to each document to be considered, for the examiner's initials; and (5) a heading that clearly indicates that the list is an information disclosure statement. These articles have been placed in the application file, but the information referred to therein has not been fully considered.

Response to Applicant's Arguments

In the response submitted by the Applicant the following 35 U.S.C § 112 rejection of claim 11 is withdrawn in light of the Applicant's cancellation of this claim.

In the response submitted by the Applicant, the 35 U.S.C § 103 (a) rejection of claims 1-5, 7 and 10 over Leskovar et al. (WO 89/09620 which has an English language equivalent document US 2002/0094542) were considered but not found persuasive.

The Applicant argues that Leskovar et al. does not teach unconjugated anthracyclines as recited in instant claim 1. The Examiner points out that claim 1 that the term "unconjugated" is no where to be found in claim 1 or dependant claims. Furthermore as the dependant claims are currently written that these "anthracyclines comprise at least one of doxorubicin, daunomycin" etc, they contain open language that includes modified anthracylines. The Applicant may believe that claims 5 and 6 are Markush type groups but the language is not correct since the accepted construction of a Markush group is "a group *consisting of* A, B or C"(M.P.E.P. § 803.02) and not "comprising at least". As currently written the dependant claims read on derivatized or modified anthracylines or platinum complexes that comprise the molecules listed in claims 5 and 6 in their structure.

The Applicant argues that Leskovar et al. teaches away from the claimed invention by "including activators of effector cells as one of the two key ingredients of the claimed invention". However as described above, such "activators of effector cells" are not excluded by the language of the claims and this argument is not commensurate in scope with the claims.

The Applicant argues that "conjugates and derivatives are two different terms" and provides two supporting references without and IDS and as such are not considered at this time. However the Applicant agues that derivatization transforms a chemical compound into a product of similar structure while conjugation of small molecules like anthracyclines to antibodies results in new antibody compounds. However common use meanings of conjugation in chemistry simply define it as "The

joining together of two compounds resulting in the formation of another compound" as supported by Biology-Online.com (Chemistry 1). Biology-online.com further define a derivative as "a chemical substance derived from another substance either directly or by modification or partial substitution" (Biology-Online.com, "derivative"). It would be obvious to one of ordinary skill in the art that a "conjugation" of two molecules is a modification of them and thus a derivative of the original molecules.

Also the argument that the conjugation of antibodies to anthracyclines changes their mechanism of action is merely the argument of counsel and is unsupported by evidence or declarations of those skilled in the art. Attorney argument is not evidence unless it is an admission, in which case, an examiner may use the admission in making a rejection. See M.P.E.P. § 2129 and § 2144.03 for a discussion of admissions as prior art. Counsel's arguments cannot take the place of objective evidence. *In re Schulze*, 145 USPQ 716 (CCPA 1965); *In re Cole*, 140 USPQ 230 (CCPA 1964); and especially *In re Langer*, 183 USPQ 288 (CCPA 1974). See M.P.E.P. § 716.01(c) for examples of attorney statements that are not evidence and that must be supported by an appropriate affidavit or declaration.

The Applicant argues that the anthracyclines used by Leskovar et al. are basically different than the claimed invention. However as described above the currently claimed invention reads on the conjugated anthracyclines of Leskovar et al. Also the Applicant argues that the enzymes taught by Leskovar are not used to treat cancer. However the entire patent of Leskovar et al. is drawn to the treatment of cancer (see Abstract). The argument that anthracyclines conjugated to antibodies are no

longer considered “anthracyclines” but "anthracydines” is not persuasive. The term “anthracydine” was not found in the supporting Application of Angelucci et al. that was used by the Examiner. Indeed since it is clear that Angelucci et al. still uses the word “anthracyclines" to describe their molecules, one of ordinary skill in the art would recognize that these antibody conjugated anthracyclines are still considered part of the group “anthracyclines”. Furthermore the Applicant's argument that Leskovar et al. distinguishes anthracyclines from their antibody conjugates is not persuasive since, the citation listed by the Applicant only mentions the antibody conjugates of anthracyclines and not anthracyclines alone (see Lescovar, paragraph 23, last 5 lines).

The Applicant argues that the Examiner has misinterpreted the Patent of Leskovar et al. and provides several alternative interpretations without any supporting references. These alternative interpretations are merely the argument of counsel and is unsupported by evidence or declarations of those skilled in the art. Attorney argument is not evidence unless it is an admission, in which case, an examiner may use the admission in making a rejection. See M.P.E.P. § 2129 and § 2144.03 for a discussion of admissions as prior art. Counsel's arguments cannot take the place of objective evidence. *In re Schulze*, 145 USPQ 716 (CCPA 1965); *In re Cole*, 140 USPQ 230 (CCPA 1964); and especially *In re Langer*, 183 USPQ 288 (CCPA 1974). See M.P.E.P. § 716.01(c) for examples of attorney statements that are not evidence and that must be supported by an appropriate affidavit or declaration.

The Applicant argues that their unexpected results overcome the rejection of obviousness. However unexpected results must be commensurate with the scope of the claims. M.P.E.P. § 716.02(d) state:

> Whether the unexpected results are the result of unexpectedly improved results or a property not taught by the prior art, the "objective evidence of nonobviousness must be commensurate in scope with the claims which the evidence is offered to support."

Since the scope of the claims are broad enough to include conjugates of anthracyclines, the Applicant has not provided evidence that anthracyclines such as these would have the same results as their unconjugated counterparts.

Therefore the following rejections stand are and are repeated below.

Claims 1-5, 7 and 10 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Leskovar et al. (WO 89/09620 of PCT/EP89/00403) in light of support by Sugiura et al. (Gann, 1982). This reference is written in German. However it has a U.S. Patent Publication (US 2002/0094542) which is a 371 and as such is an English language equivalent document (see M.P.E.P., Appendix L, 35 U.S.C. 371 National stage: Commencement.) The Examiner will cite the U.S. Patent Publication for convenience, but the rejection remains over WO 89/09620.

These claims are to a combined pharmaceutical preparation comprising as active substances: (a) at least one compound having glutaminase activity (**GA**) and (b) at least one antineoplastic agent selected from platinum complexes and anthracyclines. Claim 2 limits claim 1 by teaching the compound having GA is glutaminase, glutaminase-

asparaginase, glutaminase analog, derivative or modification of the same and is either of natural origin or is produced synthetically. Claim 3 limits that the compound with GA is from Pseudomonas. Claim 4 limit that the GA compound is modified. Claim 5 limits the type of anthracycline. Claim 7 teach the pharmaceutical preparation further comprises a pharmaceutically acceptable carrier for oral or parenteral administration.

Leskovar et al. teach a pharmaceutical preparation that comprises the Component A which includes anthracyclines such as doxorubicin and daunomycin that have been modified by conjugating them with antibodies (paragraphs 21-23). Leskovar et al. also teach that their pharmaceutical preparation can comprise antibody immunoconjugates of the enzymes asparaginase and glutaminase (paragraph 192). Leskovar et al. does not specifically teach the addition of both the anthracyclines and glutaminase enzymes in the same composition. However Leskovar et al. does teach that antibody conjugates of xenogeneic proteins can be admixed with Component A and either administered parenterally or orally and modified with PEG (polyethylene glycol) (paragraph 25-26). One of ordinary skill in the art would recognize that that a composition with active substances such as enzymes and anthracyclines would need to be mixed with a pharmaceutically acceptable carrier such as water to be administered parenterally or orally.

It would therefore have been obvious for the person of ordinary skill in the art to modify the invention of Leskovar et al. to combine an enzyme such as glutaminase with component A, which they teach as an anthracycline such as doxorubicin. Leskovar et al. provides express motivation and reasonable expectation of success by stating that

"conjugates, composed of xenogeneous proteins…can be admixed to the component A" (paragraph 26).

Furthermore it would be obvious to combine the anthracycline and glutaminase since they are two components known for the same purpose (see M.P.E.P. § 2144.06). In this case the treatment of cancer (paragraph 140 and 192). This would apply to anthracyclines that are immunoconjugated or not, since the art is replete with references that unmodified anthracyclines alone are effective against the treatment of cancer as supported by Sugiura et al. (See Table on pg 209).

While Leskovar et al. does teach the use of glutaminase and asparaginase (paragraph 192) they do not teach that the compound having glutaminase activity is *Pseudomonas* 7A glutaminase-asparaginase. However it would be obvious to one skilled in the art that any glutaminase regardless of its source will perform the same chemical reaction and can therefore be used for the same purpose unless evidence to the contrary is provided (M.P.E.P. § 2144.06).

Therefore, the invention as a whole would have been prima facie obvious at the time of filing in view of the reference listed above and as such claims 1-5, 7 and claim 10 are not allowable.

Claim 1-7 and 10 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Leskovar et al. (WO 89/09620 of PCT/EP89/00403) as applied to claim 1-5, 7 and new claim 10 above, and further in view of Housman et al. (U.S. Patent # 6,200,754, 2001).

The details of clams 1-5, 7 and 10 and their rejection are described in the above 103(a) rejection over Leskovar et al.

Claim 6 limits the pharmaceutical preparation comprising cis-platinum, oxaliplatinim or/and carboplatinum.

While Leskovar et al. teach the use of other DNA crosslinking compounds such as mitomycin C (Leskovar et al. paragraph 23) in a composition for cancer treatment he does not teach the specific use of DNA crosslinking agent cis-platinum. However Housman et al. teach that mitomycin C and cis-platinum are both DNA crosslinking agents (col 22, lines 14-15) and one of ordinary skill in the art would recognize them as common drugs for cancer treatment (col 21, line 55 to col 22, line 20). Therefore it would be obvious to replace cis-platinum or other DNA crosslinking agents such as oxaliplatinum and carboplatinum since these are art-recognized equivalents for the same purpose (M.P.E.P. § 2144.06).

Claims 1-3, 5-7, 10 and new claims 12 and 13 remain are rejected under 35 U.S.C. 103(a) as being unpatentable over Sugiura et al. (Gann, 1982).

Sugiura et al. teach a pharmaceutical preparations for in a pharmaceutical acceptable carrier (pg 208 and 209, Table II) that are administered parenterally to rats with tumors (Materials and Methods, pg 206 and 207). These compositions include anthracyclines such as Mitomycin C, adriamycin (a.k.a. doxorubicin), actinomycin D and daunomycin in carriers such as saline (Table on pg 209). Sugiura et al. also teach that their pharmaceutical preparations such as cis-platinum (a.k.a. cis-dichlorodiammine

Pt(II), pg 208) and enzymes such as glutaminase-asparaginase (page 210) in saline. Sugiura et al. does not specifically teach the addition of both the anthracyclines, cis-platinum and glutaminase enzymes in the same composition. M.P.E.P. § 2144.06 states

> "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art."

Therefore it is *prima facie* obvious to one of ordinary skill in the art to add more the anthracyclines or the *cis*-platinum compositions together into one composition of since they are all known for the same purpose.

While Sugiura et al. does teach the use of glutaminase-asparaginase (pg 210) they do not teach the source is specifically *Pseudomonas* 7A glutaminase-asparaginase. However it would be obvious to one skilled in the art that any glutaminase-asparaginase regardless of its source will perform the same chemical reaction and can therefore be used for the same purpose unless evidence to the contrary is provided (M.P.E.P. § 2144.06). Also the Acinetobacter glutaminase-asparaginase used by Sugiura et al. inherently is a tetramer of four subunits that has a molecular weight of approximatly 33 kDa which is approximately 35 kDa as supported by Holdenberg et al. (see Summary, col 1, lines 1-3).

Therefore claims 1-3, 5-7, 10, 12 and 13 remain obvious in view of the above reference.

Claims 1-7, 10, 12 and 13 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Sugiura et al. as applied to claims 1-3, 5-7, 10, 12 and 13 above, and further in view of Roberts et al. (J. Gen. Virology, 1991).

While Sugiura et al. teach the use of the enzyme **glutaminase-asparaginase** (**PGA**) to treat tumors they do not teach that PGA is modified with **polyethylene glycol** (**PEG**). Regardless this would be obvious to one of ordinary skill in the art by the time the invention was made in view of the teachings of Roberts et al. who teach that PGA half-life is increased after PEG modification (pg 304, col 1, last paragraph). It would be obvious to one of ordinary skill in the art to use the PEG modified PGA of Roberts in the composition of Sugiura et al. since this is the simple substitution of an improved version of the same enzyme that still performs the same reaction, thus having the same purpose, but has a longer half-life (M.P.E.P. § 2144.06 II and (KSR International v. Teleflex Inc. 550 U.S. ___, 127 S. Ct. 1727, 82 U.S.P.Q.2d 1385 (2007)).

Therefore claims 1-7, 10, 12 and 13 remain obvious in view of the above references.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

In response to this office action the applicant should specifically point out the support for any amendments made to the disclosure, including the claims (MPEP 714.02 and 2163.06). Due to the procedure outlined in MPEP § 2163.06 for interpreting claims, it is noted that other art may be applicable under 35 U.S.C. § 102 or 35 U.S.C. § 103(a) once the aforementioned issue(s) is/are addressed.

Applicant is requested to provide a list of all copending U.S. applications that set forth similar subject matter to the present claims. A copy of such copending claims is requested in response to this Office action.

CONTACT INFORMATION

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thane Underdahl whose telephone number is (571) 272-9042. The examiner can normally be reached Monday through Thursday, 8:00 to 17:00 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached at (571) 272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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